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Rivaroxaban for non-valvular atrial fibrillation and venous thromboembolism in the Netherlands: a real-world data based cost-effectiveness analysis

Lisa Aniek de Jong[a], Judith J. Gout-Zwart[b,c], Marina van den Bosch[d], Mike Koops[a] and Maarten J. Postma[a,e,f]

[a]Unit of PharmacoTherapy, -Epidemiology & -Economics, University of Groningen, Groningen Research Institute of Pharmacy (GRIP), Groningen, the Netherlands; [b]Department of Nephrology, University of Groningen, University Medical Center Groningen (UMCG), the Netherlands; [c]Asc Academics, Groningen, the Netherlands; [d]Bayer, Mijdrecht, the Netherlands; [e]Institute for Science in Healthy Aging & healthcaRE (SHARE), University of Groningen, University Medical Center Groningen (UMCG), Groningen, the Netherlands; [f]Department of Health Sciences, University of Groningen, University Medical Center Groningen (UMCG), the Netherlands

ABSTRACT

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) have been included in international guidelines as important alternatives to vitamin K antagonists (VKAs) for the treatment of venous thromboembolism (VTE) and stroke prevention in non-valvular atrial fibrillation (NVAF). Meanwhile, in the Netherlands, NOACs are widely used next to VKAs. The objective of this study is to estimate the cost-effectiveness of treatment with rivaroxaban compared to VKAs in NVAF and VTE patients in the Netherlands, using data from international prospective observational phase IV studies.

Methods: Two models were developed to represent NVAF and VTE patients, populated with patients from the XANTUS (NCT01606995) and XALIA (NCT01619007) international prospective observational studies. The 1-year cost-effectiveness of rivaroxaban use, compared to VKAs, was explored in a population consisting of NVAF and VTE patients (base case) as well as for four scenarios with sub-populations: NVAF patients only, VTE patients only, NVAF patients with unstable international normalized ratio (INR), and NVAF patients using an INR self-measuring device.

Results: In the base case, rivaroxaban saved €72,350 and gained 21 quality-adjusted life-years (QALYs) in a simulation of 2,000 patients over the use of VKAs. Ergo, rivaroxaban was dominant over VKAs. The probabilistic sensitivity analysis showed a probability of 85% for rivaroxaban being dominant and 100% at a willingness-to-pay threshold of €20,000/QALY. Rivaroxaban appeared to be dominant in all scenarios as well, except for the NVAF-patients-only scenario where the incremental cost-effectiveness ratio (ICER) was €157/QALY.

Conclusions: In patients with NVAF or VTE, rivaroxaban treatment is likely to be cost-effective and a potentially cost-saving alternative to VKA in the Netherlands.

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Introduction

Atrial fibrillation (AF) and venous thromboembolism (VTE) are diseases associated with blood clot formation, treated and prevented with anticoagulation therapy. Vitamin K antagonists (VKAs) are mainly used as standard anticoagulation therapy in the Netherlands. Non-vitamin K antagonist oral anticoagulants (NOACs) have been included in international guidelines as an important alternative to VKAs. The American College for Chest Physicians (ACCP) guidelines even suggested the use of NOACs over VKAs for the initial and secondary treatment of VTE in patients without cancer[1,2]. According to the medical report of the Federation of Dutch Thrombotic Services (FNT), a total of 465,107 patients are anticoagulated with either acenocoumarol or phenprocoumon (VKAs). Dutch reimbursement authorities presume the safety and efficacy of acenocoumarol, and phenprocoumon is comparable to warfarin, which is the most used VKA worldwide[3]. Recent years, however, have shown a steady increase in patients who are treated with a NOAC instead of VKAs[4].

Non-valvular atrial fibrillation (NVAF) is a disease characterized by an irregular heart rate. The arrhythmia is caused by a "circle stimulus" which leads to uncoordinated atrial activity. This causes stagnation of the blood flow in the atria, leading to blood clot formation[5]. As a result, patients who are diagnosed with NVAF have an increased risk of embolic events. NVAF doubles the risk of heart-related death and is associated with a 5-fold increased risk of a stroke[6]. Furthermore, these clots are also known to block other arteries, causing systemic embolisms (SE) or myocardial infarctions (MI)[7].

VTE is the formation of a blood clot in the veins and can be sub-divided into deep vein thrombosis (DVT) or pulmonary embolism (PE). Long-term effects of VTE can be post-

CONTACT Lisa Aniek de Jong l.a.de.jong@rug.nl Unit of PharmacoTherapy, -Epidemiology & -Economics, University of Groningen, Groningen Research Institute of Pharmacy (GRIP), Groningen, the Netherlands

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thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH)[8]. VKAs, in combination with low-molecular-weight heparins (LMWH), have been the standard anticoagulation treatment of VTE patients for decades and have proven to be very effective in preventing thromboembolic events. However, VKAs have a very narrow therapeutic window which can be impacted by many drug and food interactions. For these reasons VKAs require frequent monitoring of the international normalized ratio (INR) value of patients[4,9–11]. In the Netherlands, the INR measurement is managed and controlled by anticoagulation clinics.

In the Netherlands, NOACs have become available as a possible alternative to VKAs for prevention of stroke and systemic embolism in atrial fibrillation patients in 2012 and treatment and prevention of VTE in 2015[12,13]. Due to the predictable kinetics and pharmacodynamics of these drugs, routine coagulation monitoring is no longer required[14]. NOACs have had a prominent place in international guidelines for several years[1,15]. In September 2016, the Dutch association for general practitioners issued a statement stating that anticoagulant treatment with NOACs is equally adequate as VKAs concerning the indications AF and VTE[11]. The FNT has reported a decrease in the number of patients who started a VKA for the first time in 2015. As a reason for this decrease, the FNT states that this is mainly due to the steady increase in NOAC prescription[4].

One of these NOACs, rivaroxaban, has proven to be at least as effective and safe as VKAs in the ROCKET-AF (NCT00403767) and EINSTEIN (NCT00440193 and NCT00439777) clinical trials[16–19]. Recently, also international prospective observational studies with real-world data (RWD) have been published on the effectiveness and safety of rivaroxaban. The single-arm XANTUS (NCT01606995) study included 6,784 patients and showed low rates of stroke and major bleeding (MB) in AF patients in routine clinical practice[20]. The XALIA (NCT01619007) study included 5,136 patients and examined the efficacy and safety in VTE patients using rivaroxaban, compared to standard of care in the real-world setting. Results showed low MB rates in both treatment groups. Moreover, the use of rivaroxaban was associated with low recurrent VTE rates and shorter hospitalization compared to standard care in the real-world setting[21].

The objective of this analysis is to estimate the cost-effectiveness of treatment with rivaroxaban compared to VKA in NVAF and LMWH/VKA in VTE patients, using real-world data. Results will be compared with results from trial-based economic analyses.

Methods

For VTE and NVAF patients, two separate models were developed with a time horizon of 1 year, populated with patients from two RWD studies of rivaroxaban, XALIA (NCT01619007) and XANTUS (NCT01606995)[20,21]. The cost-effectiveness was explored in five different populations, assuming differences in costs for these groups: patients with NVAF, patients with VTE, patients with NVAF as well as patients with VTE, patients with NVAF who have unstable INR measurements and NVAF patients using INR self-measuring devices. For example, the sub-group of unstable NVAF patients is chosen separately, as these patients can be assumed to have a higher INR measurement frequency[4]. Unstable patients were assumed to have a time in therapeutic range (TTR) of $< 60\%$ which was consistent with 16% of the total hypothetical population, based on 3,978 patients in the Euro Heart Survey on AF with complete follow-up[22]. The hypothetical cohort

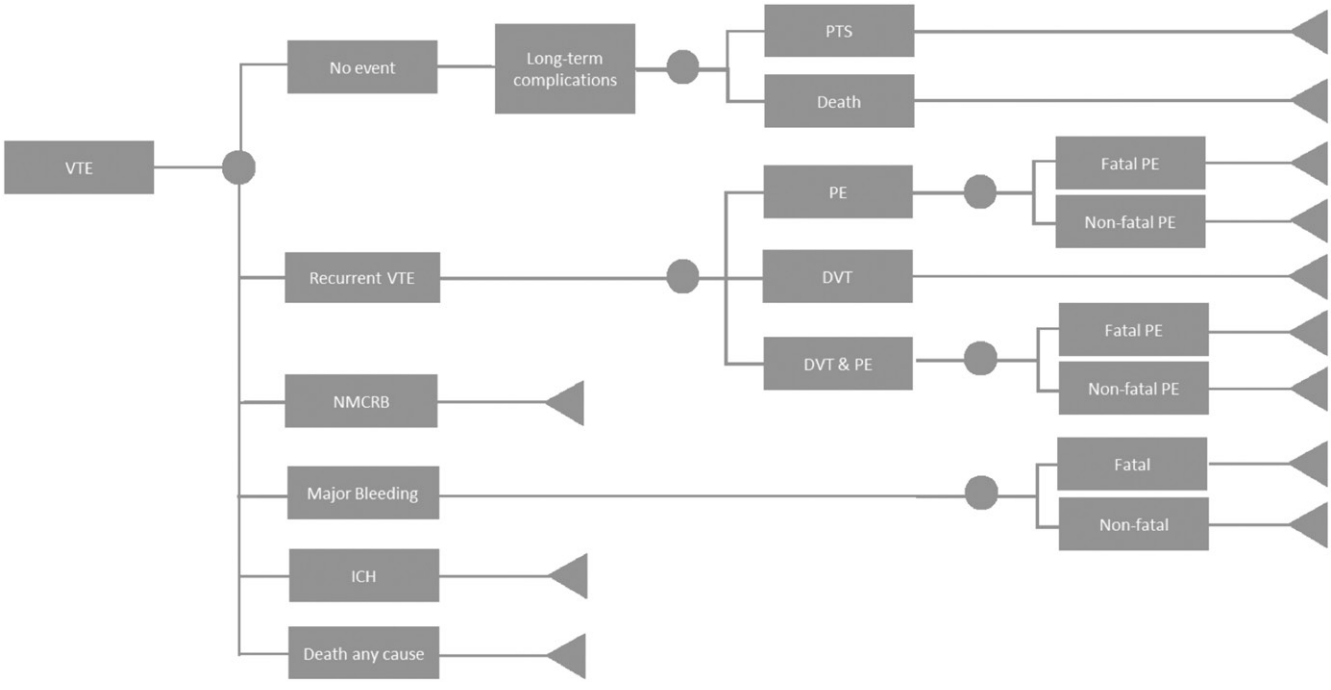

Figure 1. Progression-of-disease tree for patients with VTE. The health states for both branches of rivaroxaban and VKA therapy are identical. Abbreviations. DVT, deep vein thromboembolism; ICH, intracranial haemorrhage; NMCRB, non-major clinically relevant bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

was based on previously published trials (XALIA and XANTUS) and, therefore, a formal ethics review committee approval and consent of patients was not needed.

VTE model

Figure 1 shows the model for the VTE population. A population of 2,000 patients experiencing a VTE event entered the model and moved to no event, recurrent VTE, non-major clinically relevant bleeding (NMCRB), MB, intracranial haemorrhage (ICH), and death by any cause. Recurrent VTE was subdivided into DVT, PE, and DVT which led to PE. Because a DVT normally first leads to PE before it becomes fatal, the fatality related to DVT was not taken into account for DVT&PE patients[23]. Patients who did not experience a bleeding event, recurrent VTE, or death by any cause were assumed to be in the no event health state. In the no event health state it was assumed that 56% of the patients experienced a DVT in the past[21]. These patients were at risk of PTS. For PTS, a conservative estimation was made only accounting for severe PTS at 1% risk for "no event" patients who already experienced a DVT[24]. Patients who experienced a PE in the past could be at risk of developing CTEPH, which was conservatively not taken into account as event rates for PE as well as CTEPH are low[24], especially within the study time horizon.

Patient data from the XALIA study were used to calculate the relative risks in the model. Death by any cause was based on the all-cause mortality from the XALIA study[21]. The population in the XALIA study treated with rivaroxaban was on average 59 years of age and 55% male. The population initially treated with an unfractionated heparin (UFH), LMWH, or fondaparinux followed by VKA was on average 66 years of age and 52% male. Due to this difference, a correction was made using the propensity-scored primary outcomes of the XALIA study, as shown in Appendix Table A1[21].

All transition probabilities, for both rivaroxaban and LMWH/VKA, included in the model are based on the treatment period of 184 days, which is the duration of the XALIA study. The transition probabilities are summarized in Appendix Table A2.

NVAF model

The model for NVAF is shown in Figure 2. Data used for the transition probabilities of AF were corrected to reflect annual probabilities. Transition probabilities were based on a comparison of the XANTUS and ROCKET-AF studies[25]; therefore, we only included the health states presented in this comparative study. Patient populations of the rivaroxaban arm of both studies were matched in order to account for the differences of the real life setting and that of the clinical trial[25]. With this correction of the groups, represented as the Matching Adjusted Indirect Comparison (MAIC ratio), the rivaroxaban transition probabilities of the ROCKET-AF reflect the XANTUS results. Application of the MAIC ratio was only possible for primary end points listed by the study of Camm[25]; i.e. ischemic stroke (IS), MB, MI, vascular death, death by any cause, and no event, as shown in Figure 2.

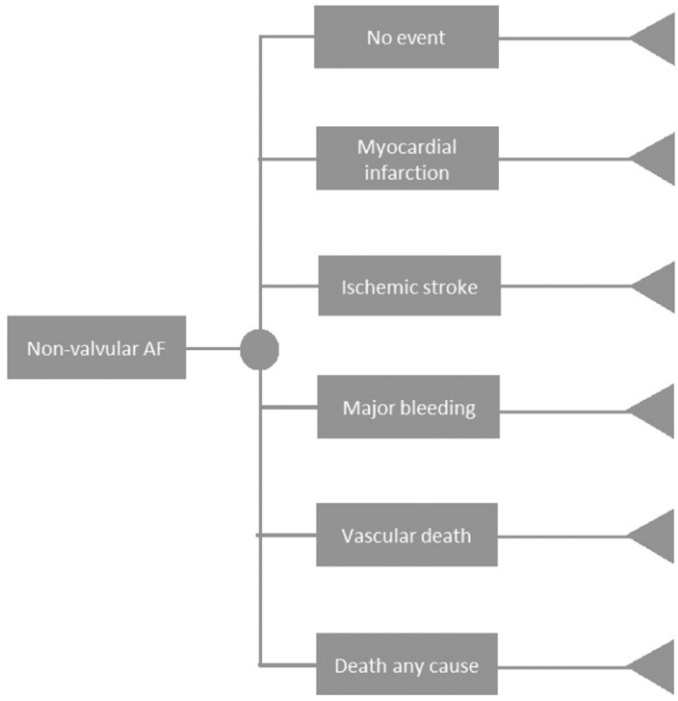

Figure 2. Progression-of-disease tree for patients with non-valvular atrial fibrillation. The health states for both branches of rivaroxaban and VKA therapy are identical. Abbreviation. AF, atrial fibrillation.

In the ROCKET-AF study, the control group is treated with warfarin, which is a VKA that is not available in the Netherlands. Because therapy with warfarin, acenocoumarol, and phenprocoumon all depend on dose adjustments based on patient INR values, their safety and efficacy are considered the same and, therefore, the ROCKET-AF study data can be considered reflective of the Dutch situation including the comparator therapy[26]. Treatment with rivaroxaban and VKA were continued during the 1-year time horizon of the model, which is line with the duration of the XANTUS trial[20].

Before adjustment, the rivaroxaban arm of the XANTUS trial comprised 60.5% of patients aged 75 years or greater and 25.5% between the age of 65 and 75. Of this same population, 50.6% had a $CHADS_2$ (Congestive Heart Failure, Hypertension, Age ($\geq$75 years), Diabetes Mellitus, prior Stroke/transient ischemic attack) score of 2, 27.6% had a score of 3, and 21.8% had a score of 4 or higher[25]. The transition probabilities in the NVAF model are shown in Appendix Table A3.

Costs

In the VTE model, NOAC treatment consisted of a 21-day course of rivaroxaban, 15 mg twice a day, followed by 20 mg once daily[10]. Costs of the LMWH were based on the costs of a daily injection of enoxaparin for 5 days, since this was the most used low-molecular-weight heparin in the RWD studies[21]. NVAF patients were treated with 20 or 15 mg rivaroxaban once daily[27]. For both models, the costs of VKAs were based on a weighted average of the use of acenocoumarol (5 mg) and phenprocoumon (3 mg) in 2014, estimated at

77% and 23%, respectively[28]. All drug costs were based on the Dutch price list (Z index) excluding 6% VAT[29].

Based on the 2015 annual medical report of the FNT, a distinction was made between measurement at the coagulation clinic, at home, and self-measurement/self-management[4]. For NVAF and VTE the INR should be within the range of 2.0–3.5. For the events of PE and DVT, the costs of PE alone were used as a conservative estimate. The costs of a vascular death were assumed to be equal to the costs of one visit to an emergency room[30]. All costs were based on the societal perspective and corrected to the year 2016. A total overview of the event-related costs is shown in Table 1.

A complete overview of the utilization and costs associated with the treatment of VKA and rivaroxaban is shown in Table 2, as well as the frequency of INR measurements per year. To calculate the mean number of INR measurements for stable or unstable NVAF patients in 1 year, the following formula is used:

The median number of correctly dosed (stable) NVAF patients is 80.2%[4].

$$A = \text{Total INR control frequency} = (\text{upper limit} - \text{lower limit}) * 80.2\% + \text{lower limit}$$

$$\text{INR control frequency stable patients} = \frac{\text{lower limit} - A}{2} + A$$

$$\text{INR control frequency unstable patients} = \frac{A - \text{lower limit}}{2} + \text{lower limit}$$

Table 1. Event costs used in cost-effectiveness analysis.

Event	Costs (fixed)	Range	Source
IS	€37,966	Fixed	Baeten et al.[37]
ICH acute	€33,378	€19,078–€51,610	Stevanovic et al.[38]
ICH annually	€14,942[a]	Fixed	Stevanovic et al.[38]
MB	€5,072	€2,033–€13,847	van Leent et al.[39]
NMCRB	€102	€76–€127	van Leent et al.[39]
MI	€5,117	€5,030–€5,203	Stevanovic et al.[40]
MI annually	€200	€186–€210	Stevanovic et al.[40]
Severe PTS	€25,550	€14,604–€39,507	Stevanovic et al.[38]
PE	€5,071	€2,533–€10,141	van Leent et al.[39]
DVT	€1,592	€796–€3,184	van Leent et al.[39]

Abbreviations. DVT, deep vein thromboembolism; ICH, intracranial haemorrhage; IS, ischemic stroke; MB, major bleeding; MI, myocardial infarction; NMCRB, non-major clinically relevant bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
[a]Average of mild, moderate, and severe ICH.

Utilities

Specific utilities were used for the baseline health state for patients suffering from NVAF or VTE. The impact of all possible health states on the patients' quality-of-life was taken

Table 2. Resource utilization and costs of NVAF and VTE.

Parameter	Mean	Range	Source
Number of INR measurements per year			
Median	20.80	15.70–27.00	FNT[4]
Stable patients	20.27		FNT[4]
Unstable patients	25.97		FNT[4]
INR measuring costs			
First quartile extra costs SM	€377.11	Fixed	NZa[30]
Monitoring SM (per quartile)	€182.84	Fixed	NZa[30]
INR control (at home)	€28.79	Fixed	NZa[30]
INR control (near-patient, per quartile)	€190.90	Fixed	NZa[30]
Travelling costs (per km)	€0.50	Fixed	
Duration of treatment (days)			
NOAC for VTE patients	184	Fixed	Ageno et al.[21]
VKA for VTE patients	179	Fixed	Ageno et al.[21]
LMWH for VTE patients	5	Fixed	Ageno et al.[21]
Drug costs			
VKA	€0.08	Fixed	ZiN[29]
LMWH	€10.50	Fixed	ZiN[41]
Rivaroxaban	€2.16	Fixed	ZiN[29]
Length of hospitalization (days)			
PE; use of LMWH/VKA	7.5	Fixed	van Bellen et al.[42]
PE; use of Rivaroxaban	6.6	Fixed	van Bellen et al.[42]
DVT; use of LMWH/VKA	7.9	Fixed	van Bellen et al.[42]
DVT; use of Rivaroxaban	6.2	Fixed	van Bellen et al.[42]
AF; use of Warfarin	3.02	Fixed	Laliberte et al.[43]
AF; use of Rivaroxaban	2.11	Fixed	Laliberte et al.[43]
Hospitalization costs			
Hospitalization costs (per day)	€447.07	Fixed	Hakkaart-van Roijen et al.[31]
Outpatient clinic costs (per visit)	€80.47	Fixed	Hakkaart-van Roijen et al.[31]
General practitioner (per visit)	€33.30	Fixed	Hakkaart-van Roijen et al.[31]
Emergency room visit (per event)	261.38	Fixed	Hakkaart-van Roijen et al.[31]
Group labile INR	16%		FNT[4]
Prevalence DVT within rVTE	56%		FNT[28]
Prevalence PE within rVTE	44%		FNT[28]
LMWH re-treatment (days)	3		FNT[4]

Abbreviations. AF, atrial fibrillation; DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anti-coagulant; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; SM, self-measurement; VKA, vitamin K antagonist; (r)VTE, (recurrent) venous thromboembolism.

Table 3. Utilities and disutilities used in the cost-effectiveness analysis.

Parameter	Mean	Range (95% CI)	Source
Venous thromboembolism			
Baseline utility VTE	0.9000	0.8566–0.9363	van Leent et al.[39]
(r)DVT (1 month)	0.8000	0.6056–0.9388	van Leent et al.[39]
Non-fatal PE (1 month)	0.6000	0.3408–0.8316	van Leent et al.[39]
Major bleeding (14 days)	0.7000	0.5006–0.8658	van Leent et al.[39]
NMCRB (2 days)	0.7000	0.6848–0.7148	van Leent et al.[39]
Minor bleeding (5 days)	0.9000	0.8200–0.9583	van Leent et al.[39]
Disutility severe PTS (lifetime)	0.0700	0.0131–0.1685	Lenert and Soetikno[44]
Atrial fibrillation			
Baseline utility AF	0.6980	0.5542–0.8242	Stevanovic et al.[40]
Stroke mild	0.6704	0.5337–0.7937	Stevanovic et al.[40]
Stroke moderate	0.6165	0.4929–0.7328	Stevanovic et al.[40]
Stroke severe	0.4416	0.3562–0.5287	Stevanovic et al.[40]
Stroke average	0.5762	Fixed	Stevanovic et al.[40]
Myocardial infarct	0.5328	0.4281–0.6360	Stevanovic et al.[40]
Disutility other ICH (6 weeks)	0.1385	0.1125–0.1666	Stevanovic et al.[40]
Disutility of NMCRB (2 days)	0.0600	0.0487–0.0722	Stevanovic et al.[40]
Medication			
Rivaroxaban	0.9730		Ahmad and Lip[45]
Vitamin K antagonists	0.9480		Robinson et al.[46]

Abbreviations. AF, atrial fibrillation; (r)DVT, (recurrent) deep vein thrombosis; ICH, intracranial haemorrhage; NMCRB, non-major clinically relevant bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

Table 4. Different populations taken into consideration for the cost-effectiveness analysis of rivaroxaban vs VKA.

Scenario	Included patient population
Base-case	VTE/NVAF
A	VTE
B	NVAF
C	NVAF without stable INR group (TTR $<$ 60%)
D	NVAF only self-measures and self-managers

Abbreviations. INR, international normalized ratio; NVAF, non-valvular atrial fibrillation; TTR, time in therapeutic range; VTE, venous thromboembolism.

into account (Table 3). Upon the occurrence of certain events a (dis)utility for a specific time range was used to calculate quality-adjusted life-years (QALYs).

Cost-effectiveness analysis

The results of the cost-effectiveness analysis are presented as the incremental cost effectiveness ratio (ICER) in costs per QALY. The ICER was calculated for each different population shown in Table 4[31]. For the base-case scenario, the ICER was calculated using a weighted average of the VTE and NVAF population, with 18.75% and 81.25% of patients experiencing VTE and NVAF, respectively[4].

Sensitivity analyses

In order to determine uncertainty around input parameters we performed a probabilistic sensitivity analysis (PSA). The distributions applied on the 95% confidence interval (CI) of the input parameters were beta for probabilities and utilities, lognormal for relative risks and differences, and gamma for costs. For the five different populations a PSA was performed using a Monte Carlo simulation with 2,000 iterations. Results were plotted in a cost-effectiveness (CE) plane with a willingness-to-pay (WTP) threshold of €20,000/QALY. Results were used to produce cost-effectiveness acceptability curves (CEACs). Additionally, a one-way sensitivity analysis was conducted to determine which parameters have the biggest influence on the ICER for the populations VTE + NVAF, VTE, and NVAF.

Results

Cost-effectiveness analysis

The deterministic results of the five populations for VKA and rivaroxaban are shown in Table 5. In the Netherlands a WTP threshold of €20,000/QALY is used for preventive treatments. Rivaroxaban was not only cost-effective at this threshold but even cost-saving in the base case and three other populations. In the base-case scenario rivaroxaban leads to health gains of 24 QALYs and savings of €71,923 per 2,000 simulated patients, compared to current standard of care with VKAs. Rivaroxaban use in scenarios A, C, and D showed a dominant ICER as well. Rivaroxaban use in NVAF patients only (scenario B) was the only non-cost-saving scenario, but is still a cost-effective option with an ICER of €157/QALY.

Sensitivity analyses

For all five populations, a probabilistic sensitivity analysis was executed with 2,000 iterations. The CE plane for the base case is shown in Figure 3. The other CE planes are presented in Appendix Figures A1–A4. Cost-effectiveness acceptability curves have been established for all five populations. The probability of being cost-effective at a WTP threshold of €20,000/QALY is 100% in the base case and all other scenarios. When a WTP threshold of €0/QALY is assumed, rivaroxaban use in the base-case scenario has a probability of 84.0% of being cost-effective compared to VKA treatment. The probabilities of cost-effectiveness for scenarios A, B, C, and D were 98.7%, 49.3%, 79.6%, and 98.2% respectively, at a WTP threshold of €0/QALY. The corresponding cost-effectiveness acceptability curves (CEAC) are displayed in Figure 4.

Table 5. Deterministic costs, effects (2,000 simulations), and incremental cost effectiveness ratios per patient of the five selected populations.

	Costs		Effects (QALY)		Incremental		
	SoC	Rivaroxaban	SoC	Rivaroxaban	Costs	Effects (QALY)	ICER
Base-case	€1.887.277	€1.815.353	672,911	696,956	–€71.923	24,045	Dominant
Scenario A	€3.100.632	€2.704.499	817,92	866,277	–€396.133	48,357	Dominant
Scenario B	€1.607.272	€1.610.166	639,447	657,882	€2.894	18,435	€157/QALY
Scenario C	€1.677.419	€1.610.166	639,447	657,882	–€67.253	18,435	Dominant
Scenario D	€1.789.302	€1.610.166	639,447	657,882	–€179.136	18,435	Dominant

Abbreviations. QALY, quality adjusted life-year; SoC, Standard of Care.

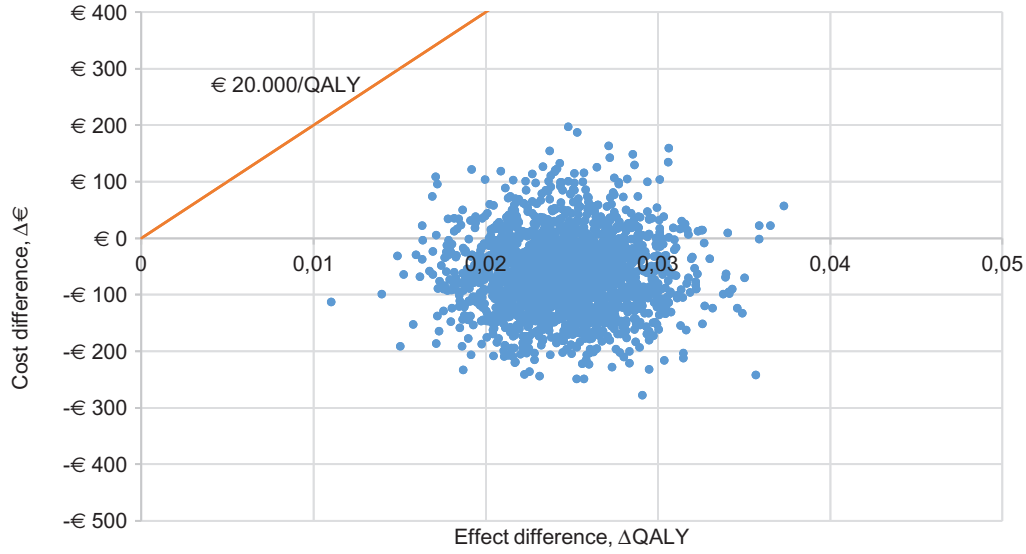

Figure 3. Probabilistic sensitivity analysis of the base-case scenario. Abbreviation. QALY, quality-adjusted life-years.

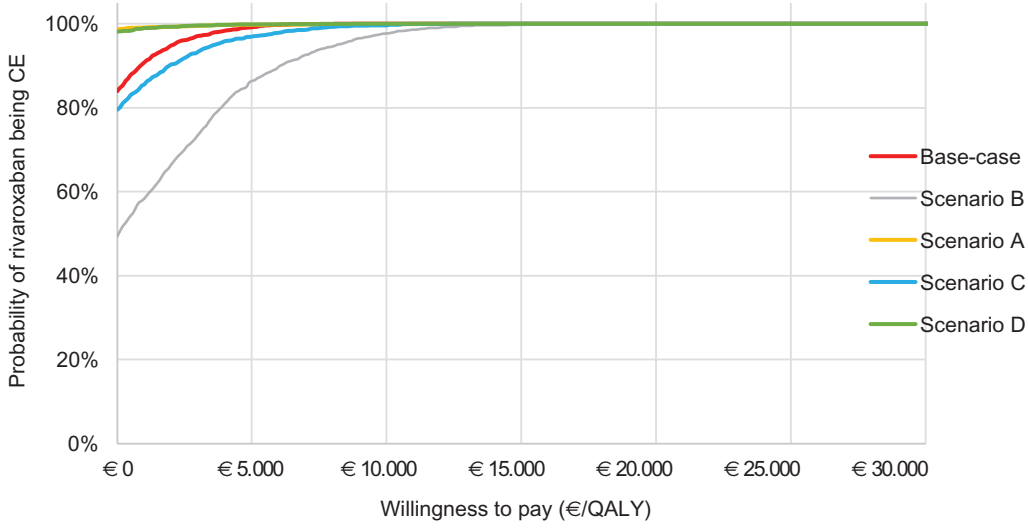

Figure 4. Cost-effectiveness acceptability curve of the base-case scenario (VTE + NVAF patients) and scenarios A, B, C, and D. Abbreviations. CE, cost-effectiveness; NVAF, non-valvular atrial fibrillation; QALY, quality-adjusted life-years; VTE, venous thromboembolism.

Results of the one-way sensitivity analysis in the base-case scenario are shown in Table 6. Tables for scenarios A and B are displayed in Appendix Tables A4 and A5. In the base-case scenario, utilities for the use of VKAs and the unit cost of rivaroxaban were the parameters with the biggest influence on the ICER.

Discussion

In the base-case analysis, rivaroxaban treatment was associated with a gain of additional 21 QALYs and saved €72,350 for 2,000 patients over a period of 1 year compared to VKA treatment. These results suggest that, in the base case,

Table 6. Results of the one-way sensitivity analysis for the base-case scenario.

Disease rates VKA—All disease rates VKA	Lower bound ICER Dominant	Upper bound ICER Dominant
Risk ratio rivaroxaban vs VKA—All disease rates VKA	€1,194*	€3,706
Baseline utilities	–€2,695	–€2,649
Utility for diseases	–€2,928	Dominant
Utility for the use of rivaroxaban	Dominated	Dominant
Utility for the use of VKA	–€1,238	€5,590*
Costs of rivaroxaban	Dominant	€19
INR measurement	–€2,991	Dominant
New patients self-measurers/self-managers (%)	–€2,979	Dominant
Disease costs	–€1,010	Dominant

Values indicated with a * are located in the southwest quadrant of the cost-effectiveness plane, meaning rivaroxaban treatment has lower costs and lower health effects than VKA treatment.
Abbreviations. ICER, incremental cost-effectiveness analysis; INR, international normalized ratio; VKA, vitamin K antagonist.

rivaroxaban is dominant over the standard treatment with a VKA for a combined population of patients with NVAF or VTE. Also in the scenarios including unstable NVAF patients and NVAF self-measurers/self-managers, the use of rivaroxaban provided cost savings and health gains compared to VKA treatment. Even though the drug costs of rivaroxaban are higher than those of VKAs, the total treatment costs are lower, due to the additional costs for INR monitoring and the relatively higher bleeding risks associated with VKA treatment. In the total NVAF population, the intervention was more costly than current treatment, at €2,894, however rivaroxaban use is still considered cost-effective with an ICER of €157/QALY.

To our knowledge this is the first Dutch economic evaluation of rivaroxaban vs VKA based on RWD studies, whereas most cost-effectiveness studies are based on clinical trial data. Our model is unique in the fact that it includes VTE and different NVAF populations in one analysis. The input parameters for the INR measurement were obtained from real-life data of the coagulation clinics, as documented in the FNT report[4]. Still, there are some uncertainties and limitations to be discussed.

The incidence proportions reported by Ageno et al.[21] are not propensity-score-adjusted, like the hazard ratios. However, we were unable to use these adjusted values, since they were only available for MB, recurrent VTE, all-cause mortality, major adverse cardiovascular events, and other thromboembolic events. The use of relative risks might have led to an over-estimation of the effect of rivaroxaban, and therefore an under-estimation of the cost-effectiveness.

The therapeutic and target range for INR in the Netherlands was not similar to the international range (2.5–3.5 vs 2.0–3.0). The FNT has recently decided to adjust the therapeutic INR range to reflect the international values[32]. Given this, we assumed that it is not necessary to extrapolate the INR values from the XANTUS, XALIA, and ROCKET-AF studies to the Dutch situation. The XANTUS study has Dutch data available, however it was not suitable for this analysis because of the absence of a control group. We compared results from the total XANTUS population[20] to the Dutch XANTUS sub-population[33], and found the number of major bleedings and thromboembolic events to be comparable (1.9% vs 2.1% and 1.6% vs 1.4%). The number of non-major bleedings was slightly lower in the total XANTUS population compared to the Dutch XANTUS sub-population: 12.9% vs 15.8%[25,33]. More non-major bleedings costs are higher, which makes the calculated ICER a conservative outcome.

The XANTUS study did not include a control group[20]. To overcome this problem, data from the analysis of Camm et al.[20] were used to make a comparison between the XANTUS and ROCKET-AF studies[16,25]. The MAIC ratio was used to convert transition probabilities of the rivaroxaban arm from the ROCKET-AF study to resemble the results in the real world. This leads to an indirect comparison which is a limitation, but, because there was no control group included in the XANTUS study, it was the only way to make a reasonable assumption[20]. Also, because the study of Camm[25] only included five primary outcomes as stated in Figure 2, the comparison was limited to these outcomes and it was not possible to include, for example, the severity of a stroke or MB (ICH vs non-ICH). These factors might have contributed to either an over- or under-estimation of the ICER in the NVAF arm of the results. On another note, it can be discussed that the 1-year time horizon might not be ideal for modelling a population suffering from NVAF, since this is a chronic disease requiring lifelong treatment and associated with significant cardiovascular complications. Therefore, a model which includes the entire lifespan of the patients suffering from NVAF might give more robust results.

The XALIA study consisted of 184 treatment days (equal to 6 months). It should be stated that 6 months of VKA treatment differs from the Dutch guidelines in which 3 months of treatment is recommended for a first episode of recurrent VTE[10]. The Dutch guideline for treatment duration of NOACs is not specific. Therefore, we remained consistent with the 6-month treatment in the XALIA study, although it might overestimate the ICER in the base case and scenario B, mainly due to increasing incremental costs, driven by the large difference in drug costs. Since there were no specified costs available for DVT&PE, a conservative estimation was made to only account for the costs of a PE, since this was the more expensive outcome of the two outcomes. This may have resulted in an under-estimation of the costs of this outcome and, therefore, an under-estimation of the ICER. Unfortunately the XANTUS study did not have a sub-group analysis of Dutch patients, therefore a similar comparison of outcomes of the NVAF model was not possible.

The results for the VTE population in this analysis are comparable with a VTE study done in the UK. In this study rivaroxaban also proved to be dominant over the standard treatment in three different treatment durations of 3, 6, and 12 months[34]. Previously, rivaroxaban was already calculated to be dominant over LMWH/VKA treatment in Dutch VTE patients, using data from the EINSTEIN clinical trials[17–19].

Our results in NVAF patients are more favourable for rivaroxaban compared to results from other studies performed in Belgium and Germany[35,36]. This might be caused by the fact that the other studies are both only based on the clinical trial data from the ROCKET-AF study and that RWD shows a more positive outcome for rivaroxaban. Another explanation could be that the drug costs of rivaroxaban have decreased substantially since these studies were published. This is a major contributor to the cost of the treatment and, for our study, we have used a cost of €2.16 per 20 mg rivaroxaban, whereas the Belgian and German studies used €2.70 and €3.26, respectively[29,35,36]. The use of €2.16 in this study is based on data from the Dutch Healthcare institute, which shows the price before a discount is agreed upon by the government and the manufacturer[29]. This makes it a conservative assumption; the price could in fact be lower, leading to an over-estimation of the ICER[13]. However, price negotiations regarding the costs associated with the coagulation clinics occur as well, which could have a negative effect on the ICER. Moreover, differences between INR values, risk factors of patients, clinical outcomes, and differences in social health costs may explain differences of cost-effectiveness results between countries.

Limitations

As with all cost-effectiveness analyses, this study has its limitations. In the real-world the initial therapy with LMWH in VTE treated patients might not be necessary, or needs to be prolonged, which is not taken into account. Moreover, treatment interruption, treatment switch, or permanent discontinuation was not taken into account. Furthermore, the health states in the model were based on the measured outcomes included in the XANTUS and XALIA trials[21,25], which were much less explicit than the outcomes included in the trials[16–18]. In the NVAF model we included the health state "vascular death", while not taking into account whether this death was caused by MI or IS. Since costs related to the patient's death might differ by cause of vascular death, this is a limitation of our model. Another point of discussion is the difference in definition of MB between the NVAF and VTE model. The XANTUS study used International Society of Thrombosis and Haemostasis (ISTH) criteria as definition for MB[25], while the XALIA study defined MB as

> overt bleeding associated with a fall in haemoglobin of 20 g/L or more; a transfusion of two or more units of packed red blood cells or whole blood; critical site bleeding (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal); or fatal bleeding [e14][21].

In the model we applied the same costs for both definitions, which might have led to over- or under-estimation of the ICER. Second, MB may differ between the VTE and NVAF models, since patient characteristics were based on the populations included in the XALIA and XANTUS trials, wherefore risk factors for bleeding events may differ between these populations. Last, we did not make a distinction between different sorts of MB. In NVAF patients, rivaroxaban is associated with decreased risk of ICH, but an increased risk of non-ICH. ICH is associated with very high (long-term) costs. Since rivaroxaban would prevent higher costs, this is a conservative assumption. Nevertheless, varying risks of MB in the one-way sensitivity analysis still showed the ICER to be cost-effective.

Conclusions

In conclusion, treatment with rivaroxaban was cost-effective or even cost-saving and provided health gains compared to the standard treatment with a VKA in Dutch NVAF and VTE patients, as well as the other examined scenarios including only VTE patients (A), only NVAF patients (B), unstable NVAF patients (C), and NVAF self-measurers (D). In the first year of treatment, rivaroxaban showed higher benefit for VTE than NVAF patients. In sensitivity analysis, the model has shown to be robust. At a WTP threshold of €20,000/QALY, rivaroxaban appeared to be 100% cost-effective in all scenarios.

Transparency

Declaration of funding

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Declaration of financial/other interests

MP has received research grants from various pharmaceutical companies, including, but not limited to, Bayer, Pfizer, Bristol-Myers Squibb, GSK, Roche, and Novartis. MB is an employee at Bayer and was involved with the start of the research, but did not influence the results and discussion. JG, LJ, and MK have no conflict of interest with relation to the subject. One peer reviewer declares their role as a co-principal investigator of the Rocket AF trial, the pivotal trial for rivaroxaban. The remaining peer reviewers for this manuscript have no conflicts of interest to disclose.

Previous presentations

Poster presentation at the 19th ISPOR European Congress 2016, Vienna, Austria: Cost-effectiveness of rivaroxaban for atrial fibrillation and venous thromboembolism in the Netherlands.

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ORCID

Lisa Aniek de Jong http://orcid.org/0000-0001-8814-0670
Maarten J. Postma http://orcid.org/0000-0002-6306-3653

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Appendix

Table A1. XALIA treatment-emergent clinical outcome results with propensity score adjustment.

Type of event	Rivaroxaban ($n = 2,505$)	SoC ($n = 2,010$)	Source
Major bleeding	19 (0.8%)	43 (2.1%)	Ageno et al.[21]
Recurrent venous thromboembolism	36 (1.4%)	47 (2.3%)	Ageno et al.[21]
All-cause mortality	11 (0.4%)	69 (3.4%)	Ageno et al.[21]
Major adverse cardiovascular events	9 (0.4%)	12 (0.6%)	Ageno et al.[21]
Other thromboembolic events	4 (0.2%)	(0.3%)	Ageno et al.[21]

Abbreviation. SoC, Standard of Care.

Table A2. Transition probabilities used in the VTE model.

Transition probability	Value (95% CI/range)		Distribution	Source
	Rivaroxaban	Vitamin K-antagonists		
Recurrent VTE and VTE related deaths				
rVTE	0.0140 (0.0098–0.0190)	0.0230 (0.0169–0.0300)	Beta	Ageno et al.[21]
non-fatal PE	0.0060 (0.0034–0.0094)	0.0071 (0.0039–0.0112)	Beta	Ageno et al.[21]
fatal PE	0.0010 (0.0002–0.0026)	0.0009 (0.0001–0.0026)	Beta	Ageno et al.[21]
DVT	0.0050 (0.0026–0.0081)	0.0124 (0.0080–0.0177)	Beta	Ageno et al.[21]
DVT & PE	0.0010 (0.0002–0.0026)	0.0018 (0.0004–0.0040)	Beta	Ageno et al.[21]
Bleeding events				
MB	0.0080 (0.0049–0.0118)	0.0210 (0.0152–0.0277)	Beta	Ageno et al.[21]
Non-fatal MB	0.0080 (0.0049–0.0118)	0.0201 (0.0144–0.0267)	Beta	Ageno et al.[21]
Fatal MB	0.0000	0.0009	Fixed	Ageno et al.[21]
NMCRB	0.1140 (0.1021–0.1264)	0.1010 (0.0886–0.1141)	Beta	Ageno et al.[21]
ICH	0.0020 (0.0007–0.0040)	0.0020 (0.0006–0.0043)	Beta	Ageno et al.[21]
Secondary outcomes				
No event	0.8580	0.8190	Fixed	Ageno et al.[21]
PTS given no event	0.0056	0.0056	Fixed	Kahn and Ginsberg[24]
Death any cause	0.0040 (0.0019–0.0068)	0.0340 (0.0265–0.0423)	Beta	Ageno et al.[21]

Abbreviations. DVT, deep venous thromboembolism; ICH, intracranial haemorrhage; MB, major bleeding; NMCRB, non-major clinically relevant bleeding; PE, pulmonary embolism; rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.

TABLE A3. Transition probabilities used in the NVAF model.

Transition probability	Value (95% CI/range)		Distribution	Source
	Warfarin	Rivaroxaban		
No event	0.9151	0.9251	Fixed	Camm[25]
IS	0.0196 (0.0165–0.0230)	0.0150 (0.0123–0.0180)	Beta	Camm[25]
MI	0.0112 (0.0089–0.0138)	0.0075 (0.0056–0.0096)	Beta	Camm[25]
MB	0.0340 (0.0299–0.0383)	0.0310 (0.0271–0.0351)	Beta	Camm[25]
Vascular death	0.0171 (0.0142–0.0202)	0.0182 (0.0152–0.0215)	Beta	Camm[25]
Death any cause	0.0030 (0.0019–0.0044)	0.0033 (0.0021–0.0047)	Beta	Camm[25]

Abbreviations. IS, ischemic stroke; MI, myocardial infarction; MB, major bleeding.

Table A4. Results of the one-way sensitivity analysis for scenario A.

	Lower bound ICER	Upper bound ICER
Disease rates VKA – Major bleed	Dominant	Dominant
Disease rates VKA – NMCR bleeding	Dominant	Dominant
Disease rates VKA – Intracranial bleeding	Dominant	Dominant
Disease rates VKA – All disease rates VKA	Dominant	Dominant
Risk ratio Rivaroxaban vs VKA – Major bleed	Dominant	Dominant
Risk ratio Rivaroxaban vs VKA – NMCR bleeding	Dominant	Dominant
Risk ratio Rivaroxaban vs VKA – Intracranial bleeding	Dominant	Dominant
Risk ratio Rivaroxaban vs VKA – All disease rates VKA	Dominant	Dominant
Baseline utility norm population	Dominant	Dominant
Utility for diseases	Dominant	Dominant
Utility for the use of Rivaroxaban	€23,812/QALY*	Dominant
Utility for the use of VKA	Dominant	Dominant
Costs of Rivaroxaban	Dominant	Dominant
INR measurement	Dominant	Dominant
New patients self-measurers/self-managers (%)	Dominant	Dominant
Disease costs	Dominant	Dominant

Values indicated with a * are located in the southwest quadrant of the cost-effectiveness plane, meaning Rivaroxaban has lower costs and lower health effects than VKAs.
Abbreviations. ICER, incremental cost-effectiveness ratio; INR, international normalized ratio; NMCR, non-major clinically relevant; QALY, quality adjusted life-year; VKA, vitamin K antagonist.

Table A5. Results of the one-way sensitivity analysis for scenario B.

	Lower bound ICER	Upper bound ICER
Disease rates VKA – Major bleed	€255	€51
Disease rates VKA – Stroke	€1,627	Dominant
Disease rates VKA – MI	€466	Dominant
Disease rates VKA – All disease rates VKA	€1,954	Dominant
Risk ratio Rivaroxaban vs VKA – Major bleed	Dominant	€1,496
Risk ratio Rivaroxaban vs VKA – Stroke	Dominant	€8,219
Risk ratio Rivaroxaban vs VKA – MI	Dominant	€1,336
Risk ratio Rivaroxaban vs VKA – All disease rates VKA	€696*	€7,008
Baseline utility AF	€198	€133
Utility for diseases	€152	€162
Utility for the use of Rivaroxaban	Dominated	€78.88
Utility for the use of VKA	€57	Dominated
Costs of Rivaroxaban	Dominant	€4,434
New patients self-measurers/self-managers (%)	€177	€137
Disease costs	€1,820	Dominant

Values indicated with a * are located in the southwest quadrant of the cost-effectiveness plane, meaning Rivaroxaban has lower costs and lower health effects than VKAs.
Abbreviations. AF, atrial fibrillation; ICER, incremental cost-effectiveness ratio; VKA, vitamin K antagonist.

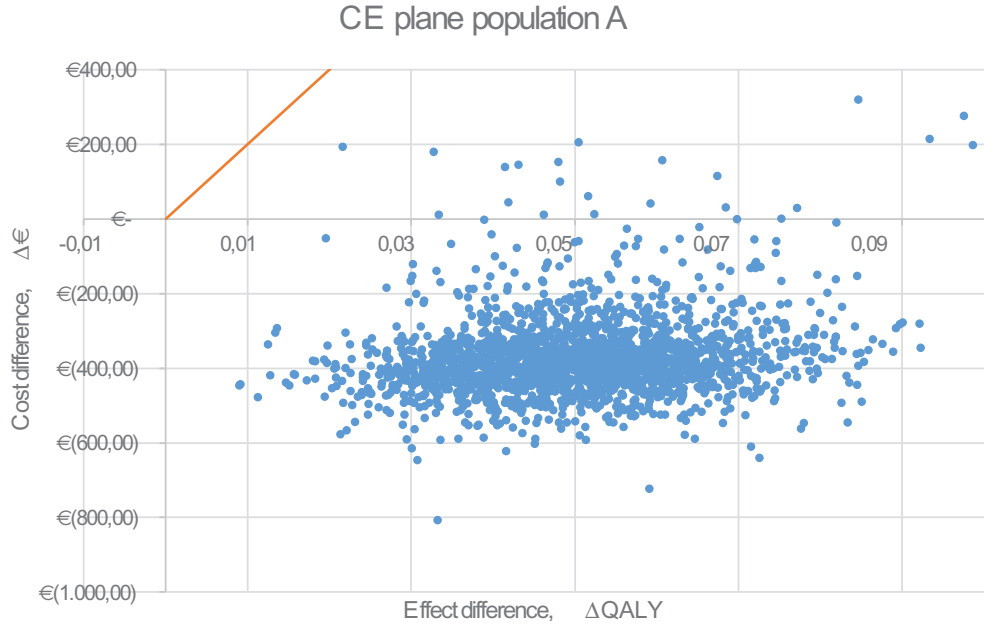

Figure A1. Probabilistic sensitivity analysis of population A, venous thromboembolism. Abbreviations. CE, cost-effectiveness; QALY, quality adjusted life-year.

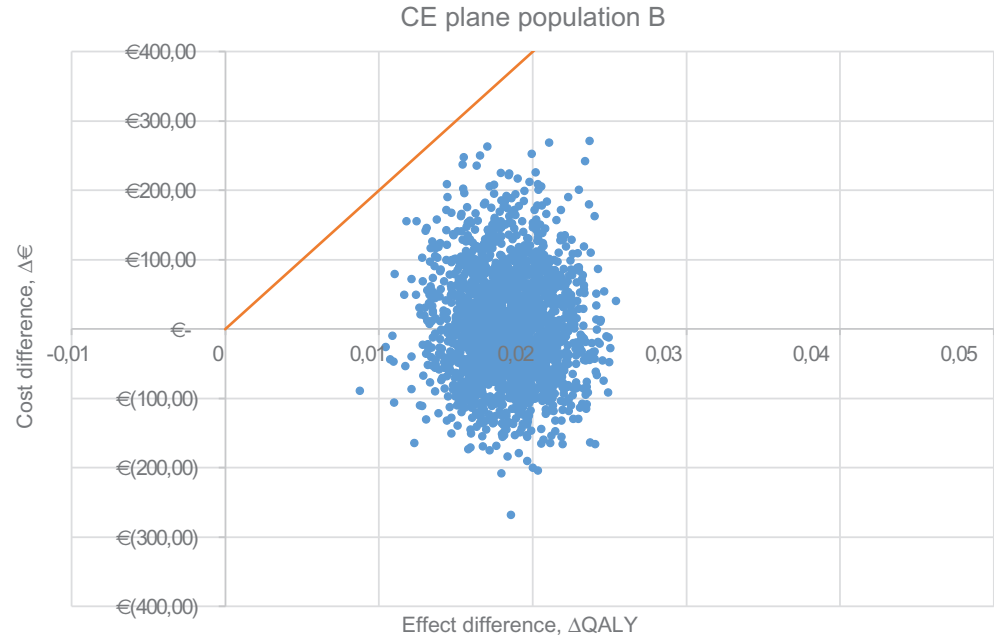

Figure A2. Probabilistic sensitivity analysis of scenario B, non-valvular atrial fibrillation. Abbreviations. CE, cost-effectiveness; QALY, quality adjusted life-year.

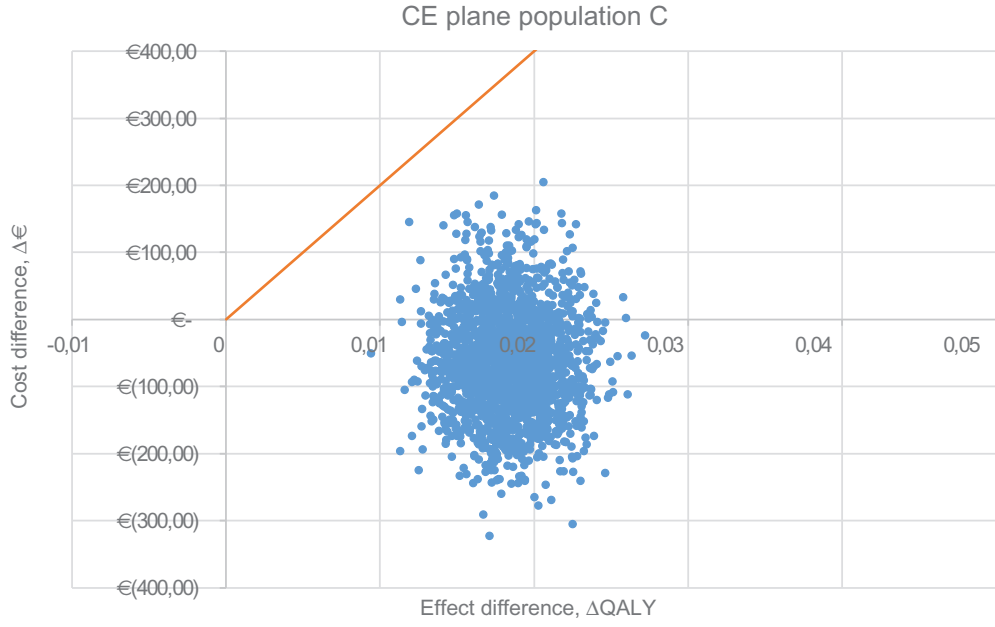

Figure A3. Probabilistic sensitivity analysis of population C, NVAF without stable INR group (TTR < 60%). Abbreviations. CE, cost-effectiveness; QALY, quality adjusted life-year.

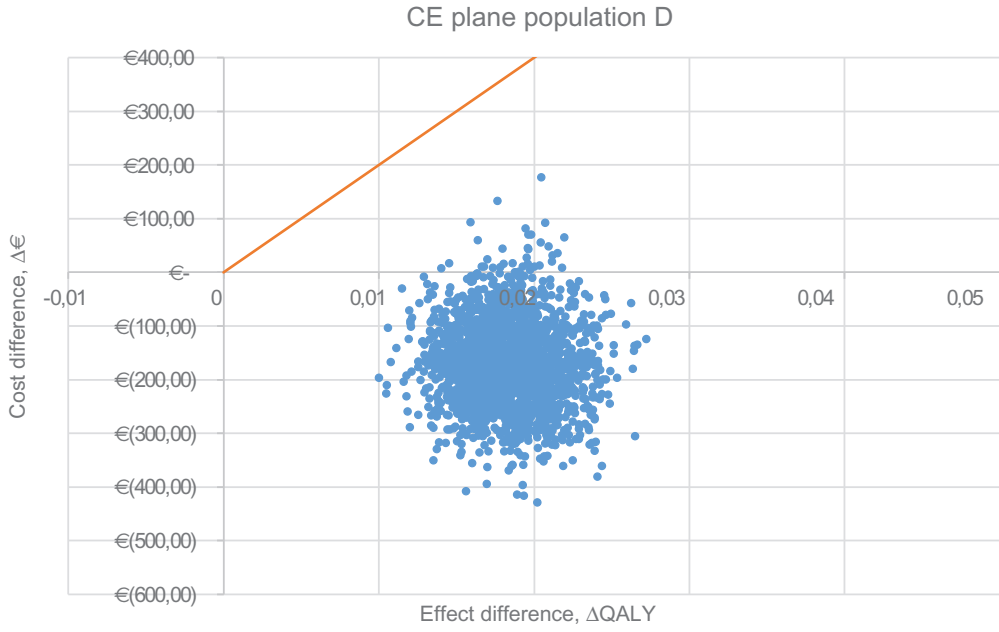

Figure A4. Probabilistic sensitivity analysis of population D, NVAF only self-measures and self-managers. Abbreviations. CE, cost-effectiveness; QALY, quality adjusted life-year.